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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,501	02/25/2004	Susan L. Acton	MPI98-052P1RDV10DV1M	3988

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MILLENNIUM PHARMACEUTICALS, INC.
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EXAMINER	
HUMPHREY, DAVID HAROLD	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/786,501	ACTON, SUSAN L.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-64* is/are pending in the application.

4a) Of the above claim(s) *61 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-60,63,64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments and Amendments

1. Claims 49-64 are pending.

Claims 49 and 55 are amended.

Claims 61 and 62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 49-60, 63, and 64 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections

Specification

3. The objection to the specification for not updating the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification is withdrawn due to Applicants' amendment to the specification.

4. The objection to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code is withdrawn due to Applicants' amendment to the specification.

Sequence Listing

5. The objection that Applicants still need to provide a statement that the paper copy and the CRF are identical and that no new matter has been introduced is withdrawn due to Applicants' arguments and submission of the copy of CRFL submitted on 02/25/04.

Title of the Invention

6. The objection to the title of the invention as not descriptive is withdrawn due to Applicants' newly submitted title.

Claim Rejections - 35 USC § 112, first paragraph

7. The rejection of claims 49-60, 63, and 64, under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is withdrawn due to Applicant's amendment to the claims.

8. The rejection of claims 49-60, 63, and 64, under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1)

known and readily available to the public; (2) reproducible from the written description is withdrawn due to Applicant's amendment to the claims.

9. The rejection of claims 49-51, 53-57, 59, 60, 63, and 64, under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an isolated antibody that binds to amino acid residues 5-164 of SEQ ID NO: 8, an isolated antibody, or fragment thereof, that specifically binds to (a) any polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 8, (b) any polypeptide encoded by the nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO: 7 or 9, does not reasonably provide enablement for an isolated antibody, or fragment thereof, that specifically binds to (c) any polypeptide encoded by a nucleic acid molecule comprising the nucleotide sequence contained in the plasmid deposited with ATCC as Accession Number 203309 is withdrawn due to Applicant's amendment to the claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. Claims 63 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 63 and 64 are vague and indefinite for the recitation of "instructions for use". It is not clear what the "instructions for use" are directed to.

11. Claims 49-54, and 63, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 49 recites an isolated antibody that specifically binds to a polypeptide that has at least 95% identity to the complete polypeptide sequence of SEQ ID NO: 8 wherein the polypeptide has kinase activity. Claim 49 additionally recites an isolated antibody which is encoded by a nucleotide sequence which is at least 95% identical to a nucleic acid comprising the sequence of SEQ ID NO: 7 or SEQ ID NO: 9 wherein the polypeptide has kinase activity.

Sequences that are less than 100% sequence identical to SEQ ID NO: 8, SEQ ID NO: 7, and SEQ ID NO: 9, encompass allelic variants, conservative substitution variants, analogs, and homologs. The written description in this instant case only sets forth SEQ ID NO: 8, SEQ ID NO: 7, and SEQ ID NO: 9. The written description is not commensurate in scope because Applicants' have not provided evidence of possession of the plethora of mutants or variants of SEQ ID NO: 2, SEQ ID NO: 7, and SEQ ID NO: 9, that are at least 95% identical **AND** have kinase activity.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. (See page 1117). The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

With the exception of the polypeptide, SEQ ID NO: 2, and the nucleic acids, SEQ ID NO: 7 and SEQ ID NO: 9, the skilled artisan cannot envision the polypeptide and the detailed structure of the encompassed polypeptides that possess kinase activity. It is possible to identify amino acid and nucleotide sequences that are at least 95% identical to SEQ ID NO: 2, 7, and 9. However, the specification has not provided a correlation between specific domain structure of the polypeptide and kinase activity. Therefore, one of ordinary skill in the art would be unable to determine which amino acids must be conserved to retain kinase activity and which amino acids could be altered. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to

disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

At the time the application was filed Applicants only had possession of SEQ ID NO: 2, and not polypeptides that share less than 100% sequence identity with SEQ ID NO: 2. The specification does not evidence the possession of all the possible mutant polypeptides that could be capable exhibiting ring-zinc-finger domains and anti-apoptotic activity. There is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

The full breadth of the claims do not meet the written description provision of 35 U.S.C. 112, first paragraph.

12. Claims 49-54, and 63, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'. " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention and the breadth of the claims: The claims are drawn to an isolated antibody that specifically binds to a polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 2, or a nucleic acid that is at least 95% identical to SEQ ID NO: 7 or SEQ ID NO:9 AND has kinase activity. Therefore, the claims encompass allelic variants, conservative substitution variants, analogs, and homologs.

The amount of direction provided by the inventor and the existence of working examples: There is limited guidance provided in the specification as only sequences that are 100% identical to SEQ ID NO: 8, SEQ ID:7 and SEQ ID NO: 9 and have kinase activity, have been presented. There is no indication as to which amino acids correlate

to the kinase domain and must be conserved to retain kinase activity. Based on the disclosure, one of ordinary skill would be able to make an isolated antibody that specifically binds to a polypeptide sequence that is at least 95% identical to SEQ ID NO: 8, but it would require undue experimentation to determine if the genus of polypeptides encompassed by the claims would also have kinase activity.

The state of the prior art and the level of predictability in the art: Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al., Journal of Cell Biology 111: 2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al., Molecular and Cellular Biology 8(3): 1247-1252, 1988).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin (see Schwartz et al., Proc Natl Acad Sci USA 84:6408-6411, 1987).

In addition, the art teaches that amino acid substitutions can have dramatic effects on a protein folding as well as enzymatic activity. Ibragimova et al. (Biophysical Journal 77: 2191-2198, 1999) teach that factors affecting protein folding and stability are governed by many small and often opposing effects and that even when the "rules" are

known for altering the stability of a protein fold by the introduction of a single point mutation the result is not reliable because the balance of forces governing folding differs for different protein sequences, and that the determination of the relative magnitude of the forces governing the folding and stability of a given protein sequence is not straightforward (page 2191, first column, lines 12-17 and second column, lines 3-8).

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation off the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results. The results of the construction of synthetic proteins remain very unpredictable as Burgess et al., Lazar et al., Schwartz et al., Lederman et al., and Ibragimova et al. conclusively demonstrate.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed inventions without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support Applicants' claim to an isolated antibody that specifically binds to a polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 2, or a nucleic acid that is at least 95% identical to SEQ ID NO: 7 or SEQ ID NO:9 **AND** has kinase activity. All of the factors considered in the sections above, underscores the criticality of providing working examples in the specification.

Quantity of experimentation needed to make or use the invention based on the content of the disclosure: In view of the Wands factors considered above, one of ordinary skill in the art would conclude that making an isolated antibody that specifically binds to a polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 2, or a nucleic acid that is at least 95% identical to SEQ ID NO: 7 or SEQ ID NO:9 **AND** has kinase activity would require undue experimentation in order to use the invention as claimed by the Applicants.

Conclusion

13. Claims 49-54, 63, and 64 are rejected. Claims 55-60 are in condition for allowance.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

David Humphrey, Ph.D.

December 8, 2006